Hans Selye and the Development of the Stress Concept[a]

Special Reference to Gastroduodenal Ulcerogenesis

SANDOR SZABO

Departments of Pathology and Pharmacology, University of California, Irvine, Pathology and Laboratory Medicine Service, VA Medical Center, Long Beach, California USA

INTRODUCTION

Biologic stress is the "nonspecific response of the body to any demand made upon it," according to the latest definition Hans Selye used in his last popular[1] and scientific books.[2] Although the designation "stress" was not used in the original short article,[3] in the 1940s it was Selye who was desperately looking for a better expression than "strain" to describe the nonspecific response of the organism. He used to emphasize the initial difficulties he encountered when he borrowed "stress" from physical sciences and engineering: People were just not ready to speak of biologic stress back when this word was used to mean only physical stress.[4] Yet, he desperately needed an expression to characterize the "new" nonspecific syndrome that can be elicited not only by physical strain but also by positive events, excitement, and even by joy.[1,5]

Thus, the development of the stress concept is linked with the discoveries of Hans Selye, his interpretation of laboratory results, and his introduction of new terms (e.g., besides stress, corticoids, glucocorticoids, and mineralocorticoids were also coined by him). This historic short review is mainly based on our previous overview[5] and the proceedings of a symposium organized and attended by his former students and coworkers.[6] It focuses on the historic background of the development of the stress concept based not only on review of the literature but also on my personal interaction as a Ph.D. student and research assistant with this great scientist. Its objective also includes an update based mainly on contributions from our laboratory on the pathogenesis of gastric, but especially duodenal, ulceration.

HISTORIC OVERVIEW

The understanding of biologic stress is closely connected to the historic role of Hans Selye in the development of this concept. Before his short article in *Nature* in 1936,[3] the neuroendocrine response to nonspecific injury was thought to be

[a]These studies were supported in part by three ROI grants and one Research Carrier Development Award from the National Institutes of Health during the last 15 years.

[b]Address for Correspondence: Dr. Sandor Szabo, Pathology & Laboratory Medicine Service (113), VA Medical Center, 5901 East 7th Street, Long Beach, CA 90822. Telephone: (562) 494-5921; Fax: (562) 494-5623.

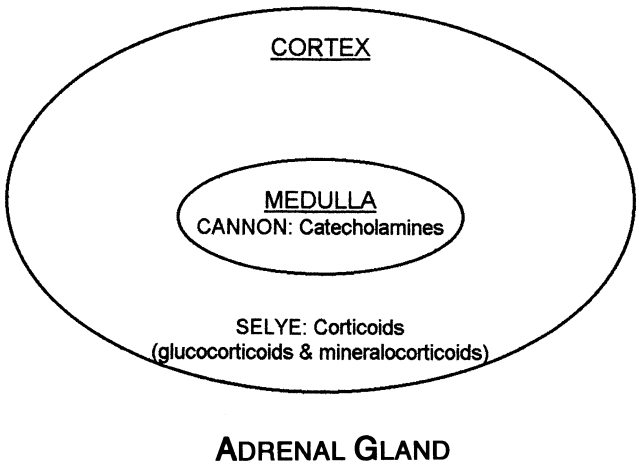

FIGURE 1. The organ-specific contributions of H. Selye and W. B. Cannon in the development of the stress concept.

restricted to the release of catecholamines, as recognized by Cannon. The early publications of Selye give full credit to Cannon, who defined the role of catecholamines in the nonspecific responses of the body to major demand or injury (FIG. 1). Selye used to complain that, whereas he gave full recognition to the adrenal medulla/Cannon connection, Cannon did not appreciate the crucial role of adrenal cortex–hypophysis axis in the stress response.[4] Selye also insisted on the nonspecificity of the neuroendocrine stress response, and he named the stress-causing agents as stressors.

The wording of a definition for stress changed over the years, but the meaning remained the same: emphasis of the revolutionary recognition that agents very diverse in nature (e.g., excessive heat or cold; forced immobilization or exercise; chemical, biologic, and psychologic agents) always elicit the same neuroendocrine (hence nonspecific) response (FIG. 2), which consists of elevated secretion of adrenocorticotrophic hormone (ACTH) by the pituitary leading to enhanced release of glucocorticoids from the adrenal cortex.[2,3,7] The neuroendocrine products, which later in the pathogenetic sequence also include other pituitary and pancreatic hormones, affect every organ system, but from the mechanistic point of view the neuroendocrine system and some immediate target organs are probably the most important. The three major changes (the "triad of stress") that are observable even macroscopically are: adrenal enlargement, gastrointestinal ulcers, and thymolymphatic atrophy.[2,3,7]

One of the historic conclusions should be, as Selye often emphasized,[4] that one can assess the structural alterations during stress without biochemical measurements. Simply weighing the thymus and the spleen or the adrenal glands in experimental animals provides quantitative indices of the intensity of stress. These indicators were used extensively in the 1940s and 1950s, and they may also serve as an approximate first approach today, although we can biochemically monitor the functions of adrenal medulla cortex, hypothalamus, and pituitary

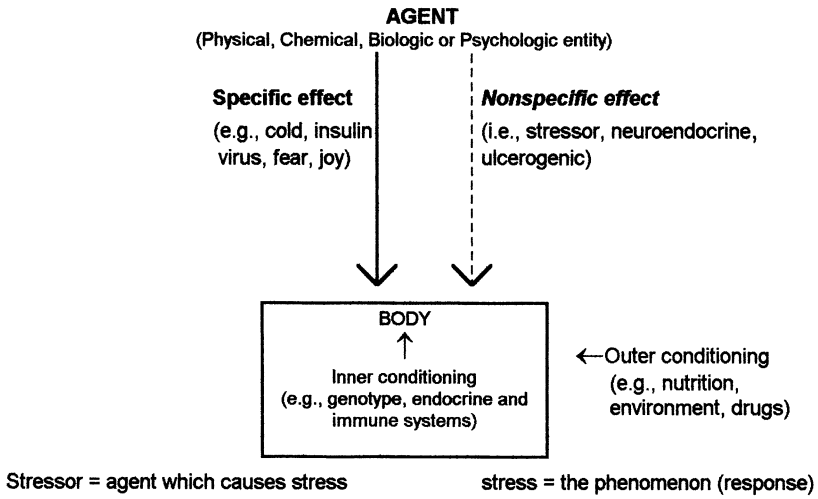

FIGURE 2. Specific and nonspecific (stressor) effects of various agents on the body. (Modified from S. Szabo[20]; used with permission from *Stress*.)

(e.g., blood or urine levels of catecholamines, corticoids, and other hormones). Monitoring stress-related gene expression is one of the most recent combinations of morphologic and quantitative approaches to stress evaluation.[8,9]

Selye's last main contribution to the stress concept was the recognition that, despite our different psychologic and cerebral reactions, both negative and positive stressors (i.e., distress and eustress) elicit virtually identical corticoid/catecholamine responses.[1,2]

STRESS AND ULCER DISEASE

In humans, stress is associated with induction or exacerbation of ulcers in the stomach; duodenum; and, according to some studies, even in the small or large intestines as well.[2,7] On the other hand, stressors in rodents affect mostly the stomach and cause only gastric erosions ("stress ulcers"). Selye used to emphasize[4] that you could kill rats with the intensity of stressors, yet the animals would develop *only* gastric and not duodenal ulcers, which are the most frequent localization of ulcers in patients. Duodenal ulcers were indeed difficult to induce until the 1970s when we found a few chemicals (e.g., propionitrile, cysteamine) that selectively induce duodenal ulcer in the rat.[10,11] We subsequently recognized a structure–activity correlation among the derivatives of propionitrile and cysteamine, and the duodenal ulcerogenic effect of certain alkyl and aryl chemicals could be predicted (FIG. 3).[12,13] Furthermore, we observed that cysteamine, which is the most potent and rapidly acting duodenal ulcerogen, exerts a profound effect on the adrenal gland, often resulting in hemorrhage and necrosis.[12,14] The duodenal ulcerogenic and adrenocorticolytic effects of terminal nitriles, amines, and thiols are correlated and depend on the number of carbons in the chain, the

nucleophilicity of terminal radicals, and probably some other physicochemical properties yet to be characterized.[12,13,15,16] Nevertheless, the duodenal ulcerogenic and adrenocorticolytic effects of these chemicals indicate that major stress organs can be selectively activated and damaged in animal models. Investigations of these changes provide new elements in the pathogenesis of ulcer disease.[15–18]

We also know from human studies, especially from the older literature in pathology (e.g., major autopsy reviews), that adrenal lesions (e.g., necrosis, adenomas) were frequently associated with ulcers in the stomach and duodenum (for reviews, see Szabo and Pfeiffer[17]). The association of adrenal changes and ulcerative colitis is scanty or doubtful.[2,19]

ENDOGENOUS MEDIATORS OF GASTRODUODENAL ULCERATION

Recent studies of the role of common and differential endogenous mediators such as dopamine, thyrotropin-releasing hormone (TRH), proteases, and growth factors provided new insights into central and peripheral pathways of gastroduodenal ulceration. Dopamine was implicated on the basis of our structure–activity studies with duodenal ulcerogens when we recognized that the common two-carbons (e.g., ethylamine side chain) may be applied not only to exogenous but to

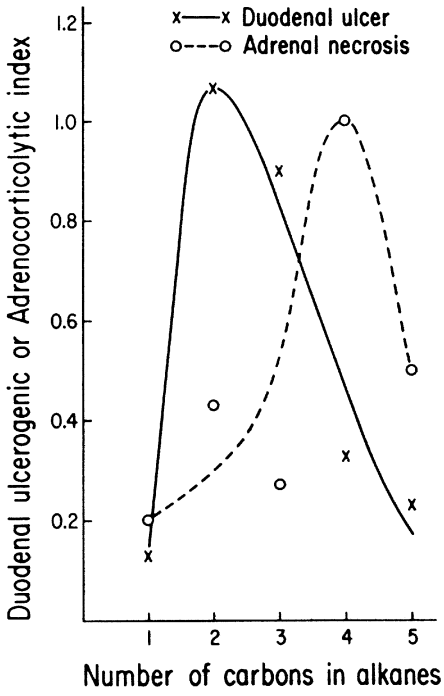

FIGURE 3. Duodenal ulcerogenic and adrenocorticolytic activities of terminal nitriles, amino and thiol alkanes. (Reproduced from S. Szabo[20]; used with permission from *Stress*.)

endogenous chemicals such as dopamine, histamine, and tyramine as well.[13,20,21] Histamine has been known to be a mediator of gastric acid secretion and its pharmacologic modulation provided the first modern and molecular mechanism of gastroduodenal ulcer treatment and prevention.[2,17] The role of dopamine was confirmed by epidemiologic investigations and laboratory research with animal models. Namely, we have found that untreated patients with dopamine deficiency (e.g., Parkinson's disease) have an excess of "peptic" ulcers, whereas dopamine receptor overactivity (e.g., in schizophrenia) provides a virtual resistance to ulcer disease.[21] Furthermore, the dopaminergic neurotoxin MPTP causes gastric *and* duodenal ulcers in rats,[22] and not only can the cysteamine-induced duodenal ulcers be prevented or aggravated by dopamine agonists or antagonists, respectively, but also the development of these experimental duodenal ulcers was preceded by depletion of dopamine in the median eminence, periventricular nucleus and, to a lesser degree, in the gastric and duodenal mucosa.[23] Numerous subsequent studies confirmed and expanded that dopamine has a protective role not only in duodenal but gastric ulceration as well.[24]

Other molecular mediators such as prostaglandins and TRH in *gastric* ulceration have been investigated by other Selye graduates, namely, A. Robert and Y. Tache.[25,26] More recently, sulfhydryls, cysteine proteases, and endothelins have been identified as new modulators of gastroduodenal ulceration in our laboratory[27–30] (TABLE 1). Monitoring the endogenous levels of these molecules *before* the mucosal lesions are visible in animal models allowed us to map the biochemical and molecular pathogenesis of *pre-ulcer* stage of not only gastric but duodenal lesions as well.[15,17,29] H. Selye would have loved to see such a breakthrough.

ULCER INDUCTION VERSUS HEALING

Among the new molecular mediators of gastroduodenal ulceration (TABLE 1), endothelins (ET) seem to have a special and dual role. Whereas most of the other endogenous chemicals play a role in the ulcer induction and development, ET seems to trigger the healing process as well. Specifically, our preliminary results indicate an early, organ- and molecular-specific duodenal release of ET-1 after administration of cysteamine but not the nontoxic and nonulcerogen ethanolamine.[29] This was followed by expression of immediate early genes (IEG) such as egr-1, c-*fos*, c-*jun*, and then by increased synthesis of basic fibroblast

TABLE 1. New Endogenous Mediators of Gastroduodenal Ulceration[a]

Hormones and Neurotransmitters	Other Chemicals
CGRP (p)	Ammonia (product of H. Pylori) (p)
Dopamine (c, p)[b]	Cysteine proteases (p)[b]
TRH(c)[b]	Endothelins (p)[b]
	Growth factors (e.g., EGF, bFGF,[b] PDGF,[b] TGF-β) (p), NO (p,c?)
	Prostaglandins (p)[b]
	Sulfhydryls (p)[b]

[a]Abbreviations: c = central (brain) actions; p = peripheral (stomach and/or duodenum) effects.

[b]First described by Selye graduates (see text & references).

growth factor (bFGF) and platelet-derived growth factor (PDGF). We described earlier that oral treatment of rats with bFGF or PDGF dose-dependently accelerated the healing of cysteamine-induced chronic duodenal ulcer.[31,32] More recently, similar treatment with vascular endothelial growth factor (VEGF) in the same animal model exhibited very strong ulcer-healing properties,[33] reinforcing the concept that vascular factors such as angiogenesis are crucial elements in ulcer healing.

Thus, a new pathway of ulcer development and healing may be chartered, emphasizing the recent recognition that the healing process may start much earlier than most of us considered likely. For example, the same mediators (e.g. ET-1) may be responsible both for duodenal ulcer initiation and triggering the healing process (FIG. 4). Cell and tissue injury in the gastrointestinal tract, like in other organs, seems to be followed by expression of IEG and stimulation of bFGF and PDGF synthesis. In the duodenum of cysteamine-treated rats, if the healing process is overcome by excess acid in the proximal duodenum, an ulcer develops and eventually heals spontaneously. The healing process may markedly be accelerated by administration of bFGF, PDGF, or VEGF.[31–33]

Major questions remain to be answered; for example, what is the reason for the high degree of organ specificity in cysteamine-induced cell and tissue injury? Is there selective uptake of cysteamine-like molecules in the duodenum and/or certain brain regions? Are there brain regions preferentially involved in ulcer pathogenesis, like in other stress-related disorders? H. Selye would have been surprised that by the end of the century, we not only have reproducible animal models of *duodenal* ulceration, but also the pathogenesis of one of the largest stress-related disorders, that is, ulcer disease, may be discussed at the molecular and cellular levels, and peripheral and central pre-ulcer pathways analyzed. These advances have mostly been achieved through the experiments initiated in his institute.

SUMMARY

Hans Selye has a historic role in the development of the stress concept. Before his short article in *Nature* in 1936, the neuroendocrine response to nonspecific injury was thought to be restricted to the release of catecholamines, as recognized by Cannon. Selye was the first to appreciate the crucial role of the adrenal cortex/hypophysis axis in the stress response. He also insisted on the nonspecificity of this neuroendocrine response, and he named the stress-causing agent "stressors." His last major contribution was the distinction between negative, that is, distress, and positive, that is, eustress reactions. The "triad of stress" (adrenal hypertrophy, gastrointestinal ulcers, thymolymphatic atrophy) was also first described by Selye, who was fascinated by the fact that in stressed rodents only gastric and not duodenal ulcers would develop. It was not until the recognition of duodenal ulcerogenic properties of propionitrile and cysteamine as well as the subsequent quantitative structure–activity studies predicting the duodenal ulcerogenic action of complex molecules that pathogenetic investigations allowed a molecular and mechanistic approach for studying the etiology and pathogenesis of duodenal ulceration. Recent studies on the role of sulfhydryls, TRH, ET, and growth factors provide new insights into central and peripheral pre-ulcer pathways. We were surprised to learn that an organ-specific ET-1 release may play a role both in ulcer induction and healing, which seems to start with the expression

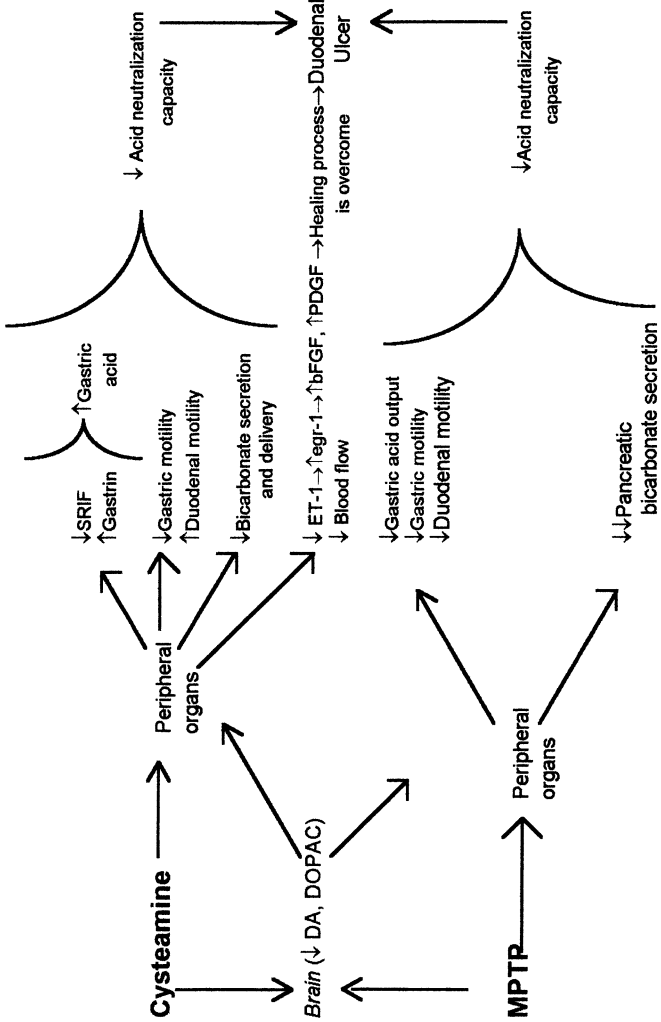

FIGURE 4. Pathogenesis of pre-ulcer stages of duodenal ulceration induced by cysteamine or the dopaminergic neurotoxin MPTP. Note the initial depletion of dopamine and interaction of increased damaging (e.g., gastric acid) and diminished protective agents (e.g., somatostatin, bicarbonate), running parallel with release of duodenal ET-1, expression of IEG such as egr-l and increased synthesis of bFGF and PDGF that is not sufficient during the first 24–48 hours; hence duodenal ulcer develops and eventually heals spontaneously. Abbreviations: DA, dopamine; DOPAC, dihydroxyphenylacetic acid; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; SRIF, somatostatin; ET-1, endothelin-1; egr-1, early growth response-1; bFGF, basic fibroblast growth factor; PDGF, platelet-derived growth factor. (Modified from S. Szabo & C. H. Cho[15]; used with permission from *Toxicology and Pathology*.

of immediate early genes such as egr-1 and stimulation of the local synthesis of growth factors such as bFGF and PDGF. Thus, a historic review originating with Hans Selye and extending through the next 60 years allows a cellular and molecular approach to the better understanding of stress-related disorders such as gastroduodenal ulceration.

ACKNOWLEDGMENTS

Most of the results from our laboratory reviewed in this article have been obtained during my 21-year affiliation with Brigham & Women's Hospital and Harvard Medical School in Boston, Massachusetts. This manuscript was prepared with the expert help of Stacey L. Dent, and her assistance is greatly appreciated.

REFERENCES

1. SELYE, H. 1974. Stress without Distress. McClelland and Stewart Ltd. Toronto.
2. SELYE, H. 1976. Stress in Health and Disease. Butterworths. Boston.
3. SELYE, H. 1936. A syndrome produced by diverse nocuous agents. Nature **138**: 32.
4. SELYE, H. Personal communication.
5. SZABO, S. 1985. Understanding biologic stress for study design and interpretation of results. Dig. Dis. Sci. **30**: 285–315.
6. 1985. Half a century of stress research: A tribute to Hans Selye by his students and associates. Experientia: **41**: 559–578.
7. SELYE, H. 1950. Stress, the Physiology and Pathology of Exposure to Stress. Acta. Montreal. Inc.
8. BULLITT, E. 1990. Expression of c-*fos*-like protein as a marker for neuronal activity following noxious stimulation in the rat. J. Comp. Neurol. **296**: 517–530.
9. PALKOVITS, M., J. S. BAFFI & S. DVORI. 1995. Neuronal organization of stress response: Pain-induced c-*fos* expression in brainstem catecholaminergic cell groups. Ann. N.Y. Acad. Sci. **771**: 313–326.
10. SZABO, S., H. SELYE. 1972. Duodenal ulcers produced by propionitrile in rats. Arch. Pathol. **93**: 389–390.
11. SELYE, H., S. SZABO. 1973. Experimental model for production of perforating duodenal ulcers by cysteamine in the rat. Nature. **244**: 458–459.
12. SZABO, S., E. S. REYNOLDS & S. H. UNGER. 1982. Structure-activity relations between alkyl nucleophilic chemicals causing duodenal ulcer and adrenocortical necrosis. J. Pharmacol. Exp. Ther. **223**: 68–76.
13. SZABO, S., H. C. HORNER & G. T. GALLAGHER. 1982. Drug-induced duodenal ulcer: Structure-activity correlations and pathogenesis. *In* Drugs and Peptic Ulcer. C. J. Pfeiffer, Ed. CRC Press. Boca Raton, FL. **2**: 55–74.
14. MCCOMB D. J., K. KOVACS, H. C. HORNER, G.T. GALLAGHER, U. SCHWEDES, K. H. USADEL & S. SZABO. 1981. Cysteamine-induced adrenocortical necrosis in rats. Exp. Mol. Pathol. **35**: 422–434.
15. SZABO S. & C. H. CHO. 1988. From cysteamine to MPTP: Structure–activity studies with duodenal ulcerogens. Toxicol. Pathol. **16**: 205–212.
16. GIAMPAOLO, C., A. T. GRAY, R. A. OLSEN & S. SZABO. 1991. Predicting chemically-induced duodenal ulcer and adrenal necrosis with classification trees. Proc. Natl. Acad. Sci. **88**: 6298–6302.
17. SZABO, S. & C. J. PFEIFFER Eds. 1989. Ulcer Disease: New Aspects of Pathogenesis and Pharmacology. CRC Press. Boca Raton, FL.

18. SZABO S., S. RIECHLIN, J. A. BOLLINER-GRUBER & A. BROWN. 1992. Somatostatin depleting potency of cysteamine-related thiols and amines in the rat: Structure activity relation. J. Pharmacol. Exp. Ther. **263**: 752–756.
19. SZABO, S. & Y. TACHE Eds. 1995. Neuroendocrinology of Gastrointestinal Ulceration. Plenum Press. New York.
20. SZABO, S. 1980. Stress and gastroduodenal ulcers. Stress **1**: 25–36.
21. SZABO, S. 1979. Dopamine disorder in duodenal ulceration. Lancet **2:** 880–882.
22. SZABO S., A. BROWN, G. PIHAN, H. DALI & J. L. NEUMEYER. 1985. Duodenal ulcer induced by MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine). Proc. Soc. Exp. Biol. Med. **180**: 567–571.
23. SZABO, S., H. C. HOMER, H. MAULL, J. SCHNOOR, C. C. CHIUEH & M. PALKOVITS. 1987. Biochemical changes in tissue catecholamines and serotonin in duodenal ulceration caused by cysteamine or propionitrile in the rat. J. Pharmacol. Exp. Ther. **240**: 871–878.
24. GLAVIN, G. B. & S. SZABO. 1990. Dopamine in gastrointestinal disease. Dig. Dis. Sci. **35**: 1153–1161.
25. ROBERT, A. 1991. Prostaglandins as regulators of gastric secretion and gastrointestinal mucosal integrity. *In* Ulcer Disease–Investigations and Basis for Therapy. E. A. Swabb & S. Szabo, Eds. Marcel Dekker. New York. Basel. 231–243.
26. TACHE, Y., H. YANG, M. YONEDA & B. BONAZ . 1995. Role of medullary TRH in vagally mediated formation of gastric lesions. *In* Neuroendocrinology of Gastrointestinal Ulceration. S. Szabo & Y. Tache, Eds. Plenum Press. New York. 161–173.
27. SZABO, S., J. S. TRIER & P. W. FRANKEL. 1981. Sulfhydryl compounds may mediate gastric cytoprotection. Science. **214**: 200–202.
28. SZABO, S., L. NAGY & M. PLEBANI. 1992. Glutathione, protein sulfhydryls and cysteine proteases in gastric mucosal injury and protection. Clin. Chim. Acta **206**: 95– 105.
29. NAGY, L., S. KUSSTATSCHER, P. V. HAUSCHKA & S. SZABO. 1996. Role of cysteine proteases and protease inhibitors in gastric mucosal damage induced by ethanol or ammonia in the rat. J. Clin. Invest. **98**: 1047–1054.
30. SZABO, S., E. R. LEVIN, A. VINCZE, A. PEDRAM, Z. SANDOR & M. JADUS. 1996. Endothelin release and expression of immediate early genes in the early stage of duodenal ulceration. Gastroenterology. **110**: A267.
31. SZABO, S., J. FOLKMAN, P. VATTAY, R. E. MORALES, G. S. PINKUS & K. KATO. 1994. Accelerated healing of duodenal ulcers by oral administration of a mutein of basic fibroblast growth factor in rats. Gastroenterology **106**: 1101–1111.
32. SZABO, S. & ZS. SANDOR. 1996. Basic fibroblast growth factor and PDGF in GI diseases. Bailliere's Clin. Gastroenterol. **10**: 97-–112.
33. SZABO, S., J. FOLKMAN, A. VINCZE, ZS. SANDOR & Z. GOMBOS. 1997. Modulation of vascular factors by VEGF/VPF (vascular endothelial cell growth factor/vascular permeability factor) is sufficient for chronic ulcer healing and acute gastroprotection. Gastroenterology **112**: A303.